IN THE UNITED STATED PATENT AND TRADEMARK OFFICE

Applicant: FERRARI M. et Al

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Title: "Process for the preparation of raloxifene hydrochloride"

DECLARATION UNDER CFR1.132

I, Massimo Ferrari, declare what follows:

I am an Italian citizen residing at Cenate Sotto (Bg), Italy,

I am familiar with the English language.

3. I further declare that:

A)EDUCATION

In 1987 I received the diploma as Qualified Chemical Technician at the Istituto Tecnico Industriale Statale (I.T.I.S) of Bergamo

In 1997 I graduated in Pharmacy at the University of Milan.

B) JOB EXPERIENCES

Since 1987 I have been working at ERREGIERRE S.p.A.

From 1987 to 1997 I worked as a Chemist in the Research and Development Department of ERREGIERRE,

Since 1997 I am the Director of the same department

I am also a co-inventor of : US6,846,950 and US7,060,838

C) EXPERIMENTAL SECTION

The following experiments were carried out under my own responsibility.

A)Preparation of 6-acetoxy –2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride (Repetition of Example 9 of US4,358,593 – Jones 1)

In a 1 litre four necks flask provided with a mechanical stirrer , thermometer and condenser, 26.3 g (0.092 mole) of 4-(2-piperidino-ethoxy)-benzoic acid N-hydrochlorate, 200 ml of 1,2-dichloroethane , 36.5 g (0.307mole) of thionyl chloride and 1 drop of N,N-dimethylformamide are added. The mixture is stirred for 2 hours at the reflux temperature of the solvent (83°C).

The reaction mixture is then concentrated under vacuum until obtaining a residue consisting of 4-(2-piperidino-ethoxy)-benzoyl chloride which is dissolved in 100 ml

of 1,2-dicloroethane.

20 g (0.0613 mole) of 6-acetoxy-2-(4-acetoxy-phenyl)-benzo[b]-thiophene are added to the solution maintained at room temperature (20-25°C) under stirring. 73.4 g of aluminium trichloride are added in 3 minute to the reaction mixture maintained under vigorous stirring at room temperature (20-25°C). During the addition of aluminium trichloride the reaction mixture assumes a dark- brownish colour and hydrochloric gas evolution is observed. The reaction mixture is thereafter left under stirring for 1 hour, then it is poured into an other 1 litre reactor flask containing a mixture of water and ice and stirred for about 15 minutes. The lower organic phase is removed , and the aqueous phase is extracted with 3x 200 ml of warm chloroform (35-40°C). The organic phase are thereafter collected and dried on 40 g. of magnesium sulphate. The solution is thereafter filtered and dried under vacuum until obtaining a brownish oil which mainly consists of 6-acetoxy –2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]-thiophene- hydrochloride.

B)Repetition of example 26 – preparation of 6-hydroxy –2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]-thiophene (raloxifene)

The oil as such as obtained in the preceding experiment is dissolved in 700 ml of methanol and the solution thus obtained is treated with 100 ml 5N of sodium hydroxide and the mixture thus obtained is stirred for 2 hours then evaporated under vacuum at a temperature not higher than 40°C, until obtaining an oily residue.

The oily residue is dissolved in 500 ml of water and the solution is washed with 2 x 500 ml diethyl of ether. The aqueous phase is acidified until about pH 2 using an aqueous solution of 50% methanesulphonic acid. In this phase the formation of a small quantity of a gummy precipitate close to the reactor walls is observed. The mixture is diluted with water until reaching a final volume of 3 litre and thereafter washed with 2x 1 litre of diethylether The aqueous phase containing the gummy precipitate is separated and placed under vacuum to remove traces of diethyl ether and brought to basic pH by addition of 30% aqueous ammonia.

The precipitation of a solid product is observed which is filtered at 20-25°C and dried under vacuum at 40°C. 15.3 g of raw raloxifene (base) with a yield based on

the intermediate 6-acetoxy-2-(4-acetoxy-phenyl)-benzo[b]-thiophene of 52.7%
The crude raloxifene (base) thus obtained is purified on a chromatographic silica gel column by using as eluting solvent 15% methanol in chloroform. The fraction containing the product (controlled elution by TLC in eluent chlorform –methanol 8:2) are collected and concentrated by evaporation until obtaining a residue formed by a foamy oil having a pale yellowish colour (13.1 g of residue), which is crystallised in 26.2 g acetone, by dissolving it in acetone at 50-55°C for 15 minutes. The mixture is cooled to 5-10°C and the precipitate is filtered on a Buchner filter. The filtered precipitate is dried under vacuum at 40°C. 12.1 g of raloxifene (base) are obtained with a yield based on the intermediate 6-acetoxy-2-(4-acetoxy-phenyl)-benzo[b]-thiophene of 41.7%.

4. I finally declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that such wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardise the validity of the applications or any patents or re-examination certificate issued thereon.

Date: July 30 ,2008

Massimo Ferrari